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(54) Title: PHARMACEUTICAL AEROSOL FORMULATION			
(57) Abstract			
<p>The present invention relates to novel pharmaceutical aerosol formulations comprising: (A) salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient, in suspension in (B) a liquefied propellant gas which is 1, 1, 1, 2, 3, 3, 3-heptafluoro-n-propane or 1, 1, 1, 2-tetrafluoropropane and mixtures thereof for administration particularly by the pulmonary route and to a process for preparing these formulations. It also relates to novel particles suitable for use in such formulations.</p>			

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Pharmaceutical aerosol formulation

The present invention relates to novel pharmaceutical aerosol formulations for the administration of salmeterol xinafoate particularly by the pulmonary route
5 and to a process for preparing these formulations. It also relates to novel particles suitable for use in such formulations.

The use of aerosols for the administration of medicaments by the peripheral aerial pathways has been known for several decades. Such aerosols generally
10 contain the therapeutic agent, one or more adjuvants such as solvents or surfactants and one or more propellants.

The most commonly used propellants in the past are chlorofluorocarbons, such as CCl_3F (Freon® 11), CCl_2F_2 (Freon® 12) or $\text{CF}_2\text{ClCF}_2\text{Cl}$ (Freon® 114).
15 However, the recent phasing out of these propellant gases due to their harmful effect on the ozone layer has caused manufacturers of aerosol sprays to use new propellant gases which protect stratospheric ozone.

Such "ozone-friendly" gases, also known as green gases, for example encompass hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons and perfluorocarbons.
20

A specific group of therapeutic agents administered by the pulmonary route are antiasthmatics including bronchodilators and antiinflammatories of steroid type having a local therapeutic action in the lungs and/or a systemic therapeutic action after absorption in the blood. 4-hydroxy- α' -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol was described as one of a wide range of bronchodilators in GB-A-2140800. This compound is also known by the generic

name of salmeterol, the xinafoate salt of which has become widely known as a highly effective treatment of inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

- 5 For medicaments such as salmeterol xinafoate, the replacement of the usual chlorofluorocarbon propellants by the novel propellants which protect the ozone layer can be accompanied by problems of stability of the suspensions. This is because the change in the polarity of the propellant sometimes results in a partial solubility of salmeterol xinafoate in the liquefied gas. This partial solubility
- 10 may lead to an undesirable increase in the size of the particles during storage and/or the formation of aggregates. Formulations of salmeterol xinafoate in hydrofluoroalkane (HFA) propellant are known to be susceptible to absorption of the drug into the rubber components of the valves of the administration device. This may then cause the valves to seize resulting in a reduction of fine particle
- 15 mass and/or the aggregates of particles will penetrate less well into the fine lower respiratory pathways, subsequently causing problems with dose uniformity.

International Patent Application No. WO 92/08446 (Glaxo Group Limited) discloses surfactant coated drug particles, however, such a formulation specifically requires a co-solvent. European Patent Application No. EP-A-0 493437 (Riker Laboratories Inc) discloses the presence of surfactants in a pharmaceutical aerosol formulation, however, the use of salmeterol xinafoate in such a formulation is not described. European Patent No. EP-A-0 556239 (Glaxo Group Limited) discloses surfactant coated medicaments, however, drying is performed by evaporation of the solvent and the use of 'spray-drying' is not described. WO 94/03153 (Glaxo Group Limited) discloses a suspension formulation of beclomethasone dipropionate, but specifically excludes the

presence of a surfactant. WO 93/11743, WO 93/11744 and WO 93/11745 (Glaxo Group Limited) also disclose suspension formulations of drugs which specifically exclude the presence of surfactant. WO 97/35562 (Danbiosyst) describes a composition of spray dried medicaments, however, polysaccharides

5 are incorporated and the use of surfactants in such a composition is not described. EP-A-257915 (Innovata) also describes a formulation comprising a spray-dried drug microcapsule, however, the use of salmeterol xinafoate in such a formulation is not described; furthermore, there is no disclosure of their use in formulations containing a liquefied propellant gas. WO 91/16882 (Liposome
10 Technology) discloses a process for spray drying a drug/lipid-containing ethanol solution, but there is no mention of employing a surfactant in this process. EP-A-550031 (Hoechst) discloses pressurised aerosol formulations containing spray-dried product, wherein the spray-dried product is obtained by spray-drying a solution of drug, surfactant and (optionally) auxiliary substance to give a finely
15 dispersed matrix, however, there is no mention of salmeterol xinafoate. International Patent Application Nos. WO 98/29096 and WO 98/29098 (Inhale Therapeutic Systems) describe the use of spray-drying a hydrophilic component and a hydrophobic component (eg. lactose), optionally stabilised by a surfactant, to provide dry powders with uniform characteristics.

20

We have now discovered that it is possible to improve the stability of suspensions of salmeterol xinafoate in the propellant by providing the drug particles with a spray-dried coating of surfactant in the absence of any other coating excipient. This protective layer apparently prevents the partial solubilization of
25 the drug in the propellant and the formation of aggregates. It is thus possible to obtain aerosol formulations for pulmonary administration which, when protected from atmospheric moisture, are stable for months and make it possible to deliver

drug particles having sizes which are sufficiently small to penetrate into the respiratory pathways.

5 A first subject of the present invention is consequently a pharmaceutical aerosol formulation comprising salmeterol xinafoate in the form of particles coated by spray-drying with surfactant in the absence of any other coating excipient in suspension in a liquefied propellant gas. A further subject of the present invention is the process for preparing these particles and pharmaceutical formulations. A still further subject are the spray-dried coated salmeterol xinafoate particles. Further subjects will become apparent to those skilled in the art from the 10 following description and examples.

The present invention thus provides a pharmaceutical aerosol formulation comprising

15 (A) salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient, in suspension in
(B) a liquefied propellant gas which is 1,1,1,2,3,3-heptafluoro-n-propane
20 or 1,1,1,2-tetrafluoroethane and mixtures thereof.

According to the present invention, the salmeterol xinafoate particles are coated with at least one surfactant. This surfactant must be physiologically acceptable when it is used by inhalation, it must also be insoluble (or essentially insoluble) 25 in the liquefied propellant gas or gases and must not have affinity therewith.

Examples of surfactants which can be used according to the present invention are anionic surfactants such as oleic acid, non-ionic surfactants such as sorbitan

trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate (Polysorbate 80), natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of ethylene oxide and of propylene oxide, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, glyceryl ricinoleate 30 OE, glyceryl ricinoleate 60 OE, cetyl alcohol, stearyl alcohol, polyethylene glycol 400 or glyceryl monolaurate, or cationic surfactants, such as cetylpyridinium chloride or benzalkonium chloride. Other examples of surfactants include synthetic phosphatides eg. distearoylphosphatidylcholine.

Preferably a single surfactant will be used.

15 Use will preferably be made of lecithin, polyoxyethylene (20) sorbitan monooleate (Polysorbate 80), sorbitan monolaurate, glyceryl ricinoleate 30 OE and glyceryl ricinoleate 60 OE. Particularly preferred surfactants include lecithin and sorbitan monolaurate. Lecithin is most especially preferred; sorbitan monolaurate is also especially preferred.

20

As indicated above the particles of salmeterol xinafoate are coated by spray-drying with at least one surfactant in the absence of any other coating excipient. In particular the use of sugars as coating excipients is avoided.

25 The propellant is preferably 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227) or 1,1,1,2-tetrafluoroethane (HFA 134a), especially 1,1,1,2-tetrafluoroethane.

The coated salmeterol xinafoate particles of the aerosol formulations of the present invention must have sizes which allow them to be administered by inhalation. The particles must be sufficiently small, on the one hand, to penetrate into the pulmonary pathways without encountering obstacles and, on the other hand, they must have a sufficiently large size to deposit in the lung and not to be carried away by exhalation. The penetration of the salmeterol xinafoate particles as far as the pulmonary bronchioli and alveoli is generally only considered possible for particles having a mean size of less than 20 μm , preferably of less than 5 μm . The size of the spray-dried coated salmeterol xinafoate particles of the present invention is preferably within the range from 0.5 μm to 10 μm , in particular from 1 μm to 5 μm .

The pharmaceutical compositions according to the invention may also comprise other pharmaceutically acceptable ingredients such as co-solvents or surfactants. In a preferred embodiment of the present invention, the formulations contain no surfactant besides that coated on the salmeterol xinafoate particles and no co-solvents.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (eg. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide, rofleponide or budesonide) or NSAIDs (eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or other beta adrenergic agents (such as salbutamol, formoterol, fenoterol or terbutaline and salts thereof) or antiinfective agents (eg. antibiotics, antivirals).

According to the invention there is most preferred a pharmaceutical aerosol formulation which consists of

- 5 (A) salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient, in suspension in
- (B) a liquefied propellant gas which is 1,1,1,2,3,3,3-heptafluoro-n-propane or 1,1,1,2-tetrafluoroethane and mixtures thereof.

10 The present invention also provides a method for preparing a pharmaceutical aerosol formulation which comprises coating salmeterol xinafoate particles by spray-drying with at least one surfactant in the absence of any other coating excipient and in packaging them, together with the propellant, in a pressurised cartridge.

15 The process for the preparation of the pharmaceutical aerosol formulation of the present invention comprises, more specifically, the stages which consist

- 20 (a) in preparing a suspension containing
- salmeterol xinafoate in the form of particles,
 - a suspending medium which is a non-solvent for salmeterol xinafoate, and
 - one or more surfactants dispersed in the suspending medium;
- (b) in spray drying the suspension obtained in stage (a), so as to obtain salmeterol xinafoate particles coated by spray-drying with the surfactant(s);
- 25 (c) in suspending the coated salmeterol xinafoate particles obtained in stage (b) in the liquefied propellant gas.

The particles of salmeterol xinafoate used in step (a) will also be of size suitable for inhalation eg. of mean size less than 20 μm (eg. 0.5 μm - 10 μm) preferably less than 5 μm (eg. 1 μm - 5 μm).

5

In one embodiment of the process of the invention, the suspension of stage (a) above is prepared by dispersing the surfactant(s) in the said suspending medium and by subsequently dispersing the salmeterol xinafoate particles in the suspension thus obtained.

10

It is also possible, according to another embodiment of the process of the invention, to adsorb, in a first step, the surfactant on the uncoated salmeterol xinafoate particles and subsequently to disperse the particle/surfactant combination in the suspending medium.

15

The suspending medium used for coating of the salmeterol xinafoate particles has to be essentially non solvent for the therapeutic agent (eg. where the solubility of salmeterol xinafoate in the suspending medium is less than around 0.1mg/ml). The preferred suspending medium is water. The content of salmeterol xinafoate in the suspension prepared in stage (a) can vary within wide limits. It is generally within the range from 1 to 40 % (mass/volume), preferably in the range from 1 to 20%, eg. 5% (mass/volume).

20

The content of surfactant in the suspension prepared in stage (a) is generally between 0.001 and 5 % by weight, preferably between 0.001 and 1 % by weight.

When the content of salmeterol xinafoate in the suspension prepared in stage (a) is around 5% (mass/volume) the content of surfactant in the dried product

25

prepared in stage (b) is generally between 0.01 and 20% by weight, preferably between 0.05 and 10% by weight.

5 The suspension described above is subsequently subjected to spray drying in an appropriate device. The suspension to be dried is dispersed as fine droplets in a stream of hot air, which instantaneously transforms them into small grains of powder. A person skilled in the art would know how to adjust the operating parameters, such as the flow rate of the suspension arriving in the drying chamber, the size of the nozzle, the inlet and outlet temperature, the atomising 10 pressure and the flow rate of the atomising air, according to the recommendations of the manufacturer and as a function of the characteristics of the product which he desires to obtain.

15 A suitable spray dryer which makes possible the drying of the salmeterol xinafoate particles of the present invention is the Büchi 191 Mini Spray Dryer (Büchi Company, Switzerland). Typical physical parameters of the atomisation in such a device which make it possible to obtain the coated particles of active principle from the suspension of stage (a) are as follows:

- 20
- Inlet air temperature: 105°C
 - Outlet air temperature: 50-70°C
 - Compressed air pressure: 7 bar
 - Atomising air flow rate: 800 NL/h
 - Drying air flow: 28m³/h

25

 - Feed flow: 4-5ml/min

wherein NL represents 'normal litre' i.e a litre of gas administered at normal temperature (25°C) and normal pressure (1 atmosphere).

The spray-dried material obtained is generally composed of particles having a mean size of between 1 μm and 10 μm and a water content of between 0.01 and 0.5 % by weight.

5

If necessary, the particles obtained by spray drying can be subjected to size reduction eg. micronisation or to any other method which is able to reduce their mean size to a value of less than 10 μm and preferably of less than 5 μm , before suspension in the propellant. Indeed, spray drying may result in partial aggregation of the particles bound to each other by the coating layer, this aggregation increasing substantially the apparent mean size of the particles. The main purpose of this step is to break up these aggregates. It is optional and its usefulness depends, of course, on the presence of aggregates, in other words on the size of the particles after spray drying.

10

15 Micronisation is carried out in devices known as compressed-air micronisers or fluid jet mills. In these devices, the particles are carried by a strong stream of air into a chamber designed so that the particles are subjected therein to a large number of impacts. In order to obtain coated salmeterol xinafoate particles having an appropriate size, these devices will be made to operate at a pressure of between 6 and 14 bar, preferably between 8 and 12 bar.

20

25 The cartridges may be filled by any means which makes it possible to obtain a homogeneous suspension of the coated salmeterol xinafoate particles in the propellant. The cartridges can be filled, for example, first with the particles and then with the propellant ('dual stage') or alternatively with a prepared suspension of the particles in the propellant ('single stage').

This filling will preferably be carried out in a controlled atmosphere with a low relative humidity, in order to limit the hydration of the particles during filling.

5 Cartridges will generally be fitted with a metering valve and a metered dose inhaler (MDI) will comprise such a cartridge and valve together with a channelling device suitable for delivery of the formulation to the lung.

10 The cartridges are preferably but not necessarily stored in a packaging composed of a film which is impermeable to atmospheric moisture. The suspensions contained in these overwrapped cartridges are expected to be stable for several months at room temperature (25°C). Other means to resist ingress of moisture to the canister may also be employed.

15 As a further aspect of the invention we present a process for the preparation of a pharmaceutical aerosol formulation according to the present invention characterised in that it comprises overwrapping filled cartridges with a film which is impermeable to atmospheric moisture.

20 A further aspect of the invention is salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient suitable for use, in combination with a propellant gas, in a pharmaceutical aerosol formulation according to the present invention.

25 As a further aspect of the invention we present salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient obtainable by a process which comprises the stages which consist

- (a) in preparing a suspension containing
- salmeterol xinafoate in the form of particles,
 - a suspending medium which is a non-solvent for salmeterol xinafoate, and
- 5 - one or more surfactants dispersed in the suspending medium;
- (b) in spray drying the suspension of the active principle obtained in stage (a), so as to obtain salmeterol xinafoate particles coated by the surfactant(s).
- 10 Cartridges containing a formulation according to the present invention also form an aspect of the invention.

Examples

The following examples are intended to illustrate the invention but do not have a limiting nature.

15

Example 1

0.2g of lecithin may be dissolved in 200 ml of demineralized water at room temperature ($20^{\circ}\text{C} \pm 2^{\circ}\text{C}$). 10g of salmeterol xinafoate as micronised particles may be dispersed under stirring in the lecithin aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.1% lecithin.

20

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer with the following parameters:

- Inlet air temperature : 105°C
- Outlet air temperature : 58°C
- 25 • Compressed air pressure : 7 bars
- Atomising air flow rate : 800 NL/h
- Drying air flow : $28 \text{ m}^3/\text{h}$

- Feed flow : 5 ml/min

The yield of the spray drying is around 70% (eg. 73%).

The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 μ m.

- 5 The spray dried material obtained may be micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

The characteristics of the particles before being placed in canisters are as follows:

- 10 mean diameter around 1.5 μ m
water content : 0.03 % (w/w)

- 15 The canisters are filled manually in a controlled atmosphere room ($20 \pm 2^\circ\text{C}$, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 2

- 1g of lecithin may be dissolved in 200 ml of demineralized water at room temperature ($20^\circ\text{C} \pm 2^\circ\text{C}$). 10 g of salmeterol xinafoate as micronised particles 20 may be dispersed under stirring in the lecithin aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.5% lecithin.

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- 25
- Inlet air temperature : 105°C
 - Outlet air temperature : 61°C
 - Compressed air pressure : 7 bars

- Atomising air flow rate : 800 NL/h
- Drying air flow : 28 m³/h
- Feed flow : 5 ml/min

The yield of the spray drying is 65%.

- 5 The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 µm.

The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

- 10 The particles before being placed in canisters have a mean diameter around 1.5 µm.

- 15 The canisters are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 3

- 20 0.2g of Montane 20 (sorbitan monolaurate) may be dissolved in 200 ml of demineralized water at room temperature (20°C ± 2°C). 10g of salmeterol xinafoate as micronised particles may be dispersed under stirring in the Montane 20 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.1% Montane 20.

- 25 This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 105°C

- Outlet air temperature : 50°C
- Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : 28 m³/h
- 5 • Feed flow : 5 ml/min

The yield of the spray drying is 69%.

The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 µm.

10 The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

The characteristics of the particles before being placed in canisters are as follows:

15 mean diameter around 1.5 µm
water content : 0.02 %

20 The canisters are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 4

0.2g of Montanox 80 (Polysorbate 80) may be dissolved in 200 ml of demineralized water at room temperature (20°C ± 2°C). 10g of salmeterol 25 xinafoate as micronised particles may be dispersed under stirring in the Montanox 80 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.1% Montanox 80.

This suspension is then spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 105°C
- Outlet air temperature : 50°C
- 5 • Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : 28 m³/h
- Feed flow : 5 ml/min

The yield of the spray drying is 75 %.

- 10 The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 µm.

The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

- 15 The particles before being placed in canisters have a mean diameter around 1.5 µm.

- 20 The canisters are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 5

- 25 0.2g of Simulsol 5817 (glyceryl ricinoleate 30 OE) may be dissolved in 200 ml of demineralized water at room temperature (20°C ± 2°C). 10g of salmeterol xinafoate as micronised particles may be dispersed under stirring in the Simulsol

5817 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.1% Simulsol 5817.

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer 5 operating with the following parameters:

- Inlet air temperature : 105°C
- Outlet air temperature : 59°C
- Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : 28 m³/h
- Feed flow : 5 ml/min

The yield of the spray drying is 78 %.

The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 µm.

15 The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

20 The particles before being placed in canisters have a mean diameter around 1.5 µm.

The canisters are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 6

0.2g of Simulsol 1285 DF (glyceryl ricinoleate 60 OE) may be dissolved in 200 ml of demineralized water at room temperature (20°C ± 2°C). 10g of salmeterol xinafoate as micronised particles may be dispersed under stirring in the Simulsol

5 1285 DF aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.1% Simulsol 1285 DF.

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- 10 • Inlet air temperature : 105°C
 • Outlet air temperature : 58°C
 • Compressed air pressure : 7 bar
 • Atomising air flow rate : 800 NL/h
 • Drying air flow : 28 m³/h
15 • Feed flow : 5 ml/min

The yield of the spray drying is 54 %.

The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 µm.

20 The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

The particles before being placed in canisters have a mean diameter around 1.5 µm.

25 The canisters are filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 7

1g of Montane 20 (sorbitan monolaurate) may be dissolved in 200 ml of demineralized water at room temperature ($20^{\circ}\text{C} \pm 2^{\circ}\text{C}$). 10 g of salmeterol xinafoate as micronised particles may be dispersed under stirring in the

5 Montane 20 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.5% Montane 20.

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- 10
- Inlet air temperature : 105°C
 - Outlet air temperature : 53°C
 - Compressed air pressure : 7 bar
 - Atomising air flow rate : 800 NL/h
 - Drying air flow : $28 \text{ m}^3/\text{h}$
 - Feed flow : 5 ml/min

15 The yield of the spray drying is 73 %.

The water content of powder is less than 0.5% (w/w). The particles before being micronised have a mean diameter between 2 and 5 μm .

The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET 20 Pharma S.A.) under a pressure of 8 bars.

The particles before being placed in canisters have a mean diameter around 1.5 μm .

25 The canisters are filled manually in a controlled atmosphere room ($20 \pm 2^{\circ}\text{C}$, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 8

5 0.5g of Montane 20 (sorbitan monolaurate) may be dissolved in 99.5ml of demineralized water at room temperature ($20^{\circ}\text{C} \pm 2^{\circ}\text{C}$). Then 5g of this solution are dissolved in 995ml of demineralized water at room temperature. 20g of salmeterol xinafoate as micronised particles are then dispersed under stirring in 400ml of this Montane 20 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.0025% Montane 20.

10 This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 105°C
- Outlet air temperature : 60°C
- Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : $28 \text{ m}^3/\text{h}$
- Feed flow : around 4 ml/min

The yield of the spray drying is around 60 %.

20 The water content of powder is 0.02% (w/w). The particles before being micronised have a mean diameter of $2.4 \mu\text{m}$.

The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

25 The characteristics of the particles before being placed in canisters are as follows:

mean diameter around $1.5 \mu\text{m}$

water content : 0.02 %

The canisters are filled manually in a controlled atmosphere room ($20 \pm 2^\circ\text{C}$, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

5

Example 9

0.5g of Montane 20 (sorbitan monolaurate) may be dissolved in 99.5ml of demineralized water at room temperature ($20^\circ\text{C} \pm 2^\circ\text{C}$). Then 10g of this solution are dissolved in 990ml of demineralized water at room temperature. 20 of salmeterol xinafoate as micronised particles are then dispersed under stirring in 400ml of this Montane 20 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.005% Montane 20.

10

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

15

- Inlet air temperature : 105°C
- Outlet air temperature : 60°C
- Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : $28 \text{ m}^3/\text{h}$
- Feed flow : around 4 ml/min

20

The yield of the spray drying is between 68 and 76 %.

The water content of powder is 0.01% (w/w). The particles before being micronised have a mean diameter of $2.3 \mu\text{m}$.

25

The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

The characteristics of the particles before being placed in canisters are as follows:

mean diameter around 1.3 μm

water content : 0.02 %

5

The canisters are filled manually in a controlled atmosphere room ($20 \pm 2^\circ\text{C}$, relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

10 **Example 10**

5g of Montane 20 (sorbitan monolaurate) may be dissolved in 95ml of demineralized water at room temperature ($20^\circ\text{C} \pm 2^\circ\text{C}$). Then 5g of this solution are dissolved in 995ml of demineralized water at room temperature. 20g of salmeterol xinafoate as micronised particles are then dispersed under stirring in 15 400ml of this Montane 20 aqueous solution. The suspension thus obtained contains 5% salmeterol xinafoate and 0.025% Montane 20.

This suspension may then be spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- 20
- Inlet air temperature : 105°C
 - Outlet air temperature : 63°C
 - Compressed air pressure : 7 bar
 - Atomising air flow rate : 800 NL/h
 - Drying air flow : $28 \text{ m}^3/\text{h}$
 - Feed flow : around 4 ml/min
- 25

The yield of the spray drying is around 77 %.

The water content of powder is 0.02% (w/w). The particles before being micronised have a mean diameter of 2.4 μm .

The spray dried material obtained is micronised in a fluid jet mill (MC 50, JET Pharma S.A.) under a pressure of 8 bars.

The characteristics of the particles before being placed in canisters are as follows:

5 mean diameter around 1.5 µm

water content : 0.02 %

The canisters are filled manually in a controlled atmosphere room (20 ± 2°C,

10 relative humidity of less than 15%) by successively introducing the micronised material and then pressurised HFA134a gas.

Example 11

0.5g of lecithin was dissolved in 99.5ml of demineralized water at room temperature. 5g of this solution was then dissolved in 995 ml of demineralized water at room temperature. 20g of salmeterol xinafoate as micronized particles were then dispersed under stirring in 400ml of this lecithin aqueous solution. The suspension thus obtained contained 5% salmeterol xinafoate and 0.0025% lecithin.

20

This suspension was then spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 105°C
- Outlet air temperature : 61°C
- Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : 28 m³/h
- Feed flow : around 4 ml/min

25

The yield of the spray drying was around 70 %.

The water content of powder was 0.01% (w/w). The particles before being micronized had a mean diameter between 2 and 5 μm .

- 5 The spray dried material obtained was micronized in a fluid jet mill (MC 50, company Jet Pharma) under a pressure of 8 bars.

The characteristics of the particles before being placed in canisters were as follows:

- 10 mean diameter around 1.5 μm
water content : 0.01 %

- 15 The canisters were filled manually in a controlled atmosphere room ($20 \pm 2^\circ\text{C}$, relative humidity of less than 15%) by successively introducing the micronized material and then pressurised HFA134a gas.

Example 12

- 20 5g of lecithin was dissolved in 95ml of demineralized water at room temperature. 5g of this solution was then dissolved in 995ml of demineralized water at room temperature. 20g of salmeterol xinafoate as micronized particles were then dispersed under stirring in 400 ml of this lecithin aqueous solution. The suspension thus obtained contained 5% salmeterol xinafoate and 0.025% lecithin.

- 25 This suspension was then spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:
- Inlet air temperature : 105°C
 - Outlet air temperature : 60°C

- Compressed air pressure : 7 bar
 - Atomising air flow rate : 800 NL/h
 - Drying air flow : 28 m³/h
 - Feed flow : around 4 ml/min
- 5 The yield of the spray drying was around 75 %.
The water content of powder was 0.01% (w/w). The particles before being micronized had a mean diameter between 2 and 5 µm.
- 10 The spray dried material obtained was micronized in a fluid jet mill (MC 50, company Jet Pharma) under a pressure of 8 bars.
The characteristics of the particles before being placed in canisters were as follows:
mean diameter around 1.5 µm
15 water content : 0.01 %
- 20 The canisters were filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronized material and then pressurised HFA134a gas.
- 25 **Example 13**
5g of lecithin was dissolved in 95ml of demineralized water at room temperature. 10g of this solution was then dissolved in 990ml of demineralized water at room temperature. 20g of salmeterol xinafoate as micronized particles were then dispersed under stirring in 400ml of this lecithin solution. The suspension thus obtained contained 5% salmeterol xinafoate and 0.05% lecithin.

This suspension was then spray-dried in a Büchi 191 Mini Spray Dryer operating with the following parameters:

- Inlet air temperature : 105°C
- Outlet air temperature : 60°C
- 5 • Compressed air pressure : 7 bar
- Atomising air flow rate : 800 NL/h
- Drying air flow : 28 m³/h
- Feed flow : around 4 ml/min

The yield of the spray drying was around 75 %.

10 The water content of powder was 0.01% (w/w). The particles before being micronized had a mean diameter between 2 and 5 µm.

The spray dried material obtained was micronized in a fluid jet mill (MC 50, company Jet Pharma) under a pressure of 8 bars.

15 The characteristics of the particles before being placed in canisters were as follows:

mean diameter around 1.5 µm

water content : 0.01 %

20 The canisters were filled manually in a controlled atmosphere room (20 ± 2°C, relative humidity of less than 15%) by successively introducing the micronized material and then pressurised HFA134a gas.

25 Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

Claims

1. A pharmaceutical aerosol formulation comprising:

5 (A) salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient, in suspension in
(B) a liquefied propellant gas which is 1,1,1,2,3,3,3-heptafluoro-n-propane or 1,1,1,2-tetrafluoroethane and mixtures thereof.

10 2. A pharmaceutical aerosol formulation according to claim 1 which consists of

15 (A) salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient, in suspension in
(B) a liquefied propellant gas which is 1,1,1,2,3,3,3-heptafluoro-n-propane or 1,1,1,2-tetrafluoroethane and mixtures thereof.

20 3. A pharmaceutical aerosol formulation according to claim 1 or claim 2, characterised in that said surfactant is chosen from oleic acid, non-ionic surfactants such as sorbitan trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate (Polysorbate 80), natural lecithin, oleyl polyoxyethylene (2) ether, 25 stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of ethylene oxide and of propylene oxide, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate,

glyceryl ricinoleate 30 OE, glyceryl ricinoleate 60 OE, cetyl alcohol, stearyl alcohol, polyethylene glycol 400 or glyceryl monolaurate, or cationic surfactants, such as cetylpyridinium chloride or benzalkonium chloride.

5 4. A pharmaceutical aerosol formulation according to any one of claims 1 to 3, characterised in that a single surfactant will be used.

10 5. A pharmaceutical aerosol formulation according to claim 4, characterised in that the single surfactant is chosen from lecithin, polyoxyethylene (20) sorbitan monooleate (Polysorbate 80), sorbitan monolaurate, glyceryl ricinoleate 30 OE or glyceryl ricinoleate 60 OE.

15 6. A pharmaceutical aerosol formulation according to claim 4 or claim 5, characterised in that the single surfactant is chosen from lecithin and sorbitan monolaurate.

7. A pharmaceutical aerosol formulation according to any one of claims 1 to 6, characterised in that the propellant is 1,1,1,2-tetrafluoroethane.

20 8. A pharmaceutical aerosol formulation according to any one of claims 1 to 7, characterised in that the mean size of the coated salmeterol xinafoate particles is within the range from 0.5 to 10 µm.

25 9. A pharmaceutical aerosol formulation according to claim 8, characterised in that the mean size of the coated salmeterol xinafoate particles is within the range from 1 to 5 µm.

10. A pharmaceutical aerosol formulation according to any one of claims 1 to 9, characterised in that the formulation contains no surfactant besides that coated on the salmeterol xinafoate particles and no co-solvents.

5 11. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 1 to 10, characterised in that it comprises the stages which consist

10 (a) in preparing a suspension containing

- salmeterol xinafoate in the form of particles,
- a suspending medium which is a non-solvent for salmeterol xinafoate,
and

- one or more surfactants dispersed in the suspending medium;

15 (b) in spray drying the suspension obtained in stage (a), so as to obtain salmeterol xinafoate particles coated by spray-drying with the surfactant(s);

(c) suspending the coated salmeterol xinafoate particles obtained in stage (b) in the liquefied propellant gas.

20 12. A process for the preparation of a pharmaceutical aerosol formulation according to claim 11, characterised in that it comprises an additional stage of size reduction of the coated particles obtained by spray drying before suspension in the propellant.

25 13. A process for the preparation of a pharmaceutical aerosol formulation according to claim 11 or claim 12, characterised in that the mean size of the coated drug particles is within the range from 0.5 to 10 μ m.

14. A process for the preparation of a pharmaceutical aerosol formulation according to claim 13, characterised in that the mean size of the coated drug particles is within the range from 1 to 5 μ m.

5 15. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 11 to 14, characterised in that the suspending medium is a medium which is a non-solvent for salmeterol xinafoate.

10 16. A process for the preparation of a pharmaceutical aerosol formulation according to claim 15, characterised in that the suspending medium is water.

15 17. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 11 to 16, characterised in that the suspension of stage (a) is prepared by dispersing the surfactant(s) in the said suspending medium and by subsequently dispersing the salmeterol xinafoate particles in the colloidal solution thus obtained.

20 18. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 11 to 17, characterised in that the content of salmeterol xinafoate in the suspension prepared in stage (a) is within the range from 1 to 40 % (mass/volume).

25 19. A process for the preparation of a pharmaceutical aerosol formulation according to claim 18, characterised in that the content of salmeterol xinafoate in the suspension prepared in stage (a) is in the range from 1 to 20% (mass/volume).

20. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 11 to 19, characterised in that the content of surfactant in the suspension prepared in stage (a) is between 0.001 and 5 % by weight.

5

21. A process for the preparation of a pharmaceutical aerosol formulation according to claim 20, characterised in that the content of surfactant in the suspension prepared in stage (a) is between 0.001 and 1 % by weight.

10

22. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 11 to 21, characterised in that it comprises successively filling cartridges with the particles obtained after spray drying or micronisation and then with the propellant.

15

23. A process for the preparation of a pharmaceutical aerosol formulation according to any one of claims 11 to 22, characterised in that it comprises filling cartridges in a single stage by introduction of a suspension of the coated particles, which are obtained after spray drying or micronisation, in the propellant.

20

24. A process for the preparation of a pharmaceutical aerosol formulation according to claim 22 or claim 23, characterised in that it comprises overwrapping filled cartridges with a film which is impermeable to atmospheric moisture.

25

25. Salmeterol xinafoate in the form of particles coated by spray-drying with at least one surfactant in the absence of any other coating excipient suitable for

use, in combination with a propellant gas, in a pharmaceutical aerosol formulation according to any one of claims 1 to 10.

26. Salmeterol xinafoate in the form of particles coated by spray-drying with

5 at least one surfactant in the absence of any other coating excipient obtainable by a process which comprises the stages which consist

(a) in preparing a suspension containing

- salmeterol xinafoate in the form of particles,

10 - a suspending medium which is a non-solvent for salmeterol xinafoate, and

- one or more surfactants dispersed in the suspending medium;

(b) in spray drying the suspension of the active principle obtained in stage
15 (a), so as to obtain salmeterol xinafoate particles coated by the surfactant(s).

27. A pharmaceutical aerosol formulation obtainable by a process according to any one of claims 11 to 24.

20 28. A cartridge containing a pharmaceutical aerosol formulation according to any one of claims 1 to 10 and 27.

29. A cartridge according to claim 28 overwrapped with a film which is impermeable to atmospheric moisture.

INTERNATIONAL SEARCH REPORT

International Application No.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/16 A61K31/137

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
TPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal WPI Data PAI BIOSIS CHEM ABS Data MEDLINE EMBASE

6. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 08447 A (GLAXO GROUP LTD) 29 May 1992 (1992-05-29)	1-7,10, 25-29
	cited in the application	
A	page 1, paragraph 4 -page 2, paragraph 3	11-24
	page 3, paragraph 7	
	page 7, paragraph 3 - paragraph 4; claims	
	1-11; examples 1,3,4	

X	EP 0 655 237 A (HOECHST AG)	1-6,10,
	31 May 1995 (1995-05-31)	11,15,
	---	22,25-27
	page 2, column 2, last paragraph -page 3,	
	column 3, paragraph 1	
	page 3, column 3, last paragraph - line 26	
	page 4, column 5, line 29 - line 34	
	page 4, column 5, line 52 - line 54;	
	claims; examples	

	-/-	

Further documents are listed in the continuation of box C.

Patient family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 00/01418

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WO 99 53901 A (LOUIS OLIVIER ; LLORCA NATHALIE (FR); ROSIER PATRICK (FR); CAVAILLO) 28 October 1999 (1999-10-28)</p> <p>page 2, paragraph 1 – paragraph 2</p> <p>page 3, paragraph 1 –page 4, paragraph 4</p> <p>page 5, last paragraph –page 7, paragraph 4</p> <p>page 7, last paragraph –page 8, line 17;</p> <p>claims 1-3,9-11,14-17,20-31,34-43; example 14</p> <p>-----</p>	1,3-24, 27-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte
lional Application No
PCT/GB 00/01418

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9208447	A 29-05-1992	AT 127012	T	15-09-1995
		AU 653369	B	29-09-1994
		AU 8862991	A	11-06-1992
		CA 2094727	A	10-05-1992
		DE 69112635	D	05-10-1995
		DE 69112635	T	08-02-1996
		DK 556239	T	06-11-1995
		EP 0556239	A	25-08-1993
		ES 2078550	T	16-12-1995
		GR 3018171	T	29-02-1996
		JP 6501693	T	24-02-1994
		US 5785952	A	28-07-1998
EP 0655237	A 31-05-1995	AU 676390	B	06-03-1997
		AU 7905194	A	08-06-1995
		CA 2136704	A	28-05-1995
		FI 945524	A	28-05-1995
		HU 75152	A	28-04-1997
		JP 7187996	A	25-07-1995
		NO 944526	A	29-05-1995
		NZ 264993	A	26-03-1996
		ZA 9409378	A	11-08-1995
WO 9953901	A 28-10-1999	AU 3523199	A	08-11-1999